Katsuhiko Mikoshiba delivers 2013 Rodbell Lecture

By Sheila Yong

The prestigious Dr. Martin Rodbell Lecture Series Seminar April 30 went international this year with Katsuhiko Mikoshiba, M.D., Ph.D., as its fifteenth speaker. In his talk on the "Role of IP3 receptor signaling in development, cell function, and diseases," Mikoshiba discussed how he discovered the inositol 1,4,5-triphosphate (IP3) receptor, and his ongoing quest in characterizing the protein.

Mikoshiba said it has been more than 20 years since his last visit to the NIEHS, and he was excited to meet with researchers and some of his longtime friends to exchange research ideas. (Photo courtesy of Steve McCaw)

Mikoshiba *(http://www.brain.riken.jp/en/faculty/details/29)* is currently the senior team leader of the developmental neurobiology team at RIKEN Brain Science Institute.

Host James Putney, Ph.D., head of the NIEHS Calcium Regulation Group in the Laboratory of Signal Transduction, compared Mikoshiba's scientific career with that of Rodbell. "Dr. Mikoshiba's career path is very similar to that of Dr. Rodbell in that both of these scientists made an observation very early on that they did not initially understand. Nonetheless, with relentless dedication, they subsequently developed them into the definition of the entire field of biomedical research."

The discovery of IP3 receptor

When IP3 was first shown to trigger calcium release from inside the cells, many researchers, including Mikoshiba, became interested in determining how this release is regulated. "Calcium ions, though essential for normal cell function, are detrimental when present at excessive levels," he explained. "Therefore, understanding how the internal calcium levels are regulated is important for determining how certain abnormalities that affect calcium signaling result in disease."

Rodbell's widow and honored guest, Barbara, center, has attended every Rodbell lecture. Seated with her is NIEHS and NTP Director Linda Birnbaum, Ph.D., left, who complimented Mikoshiba for his clear and coherent presentation. (Photo courtesy of Steve McCaw)

Mikoshiba stayed with what he knows best — the brain. While a postdoctoral fellow with Jean-Pierre Changeux, Ph.D., he had observed that mice lacking the P400 protein exhibited severe defects in the development of Purkinje cells, one of the largest neurons in the brain. As a result, these mice suffered from an inability to coordinate muscle movements.

As a young principal investigator at the time, with only two lab members, Mikoshiba spent more than two years screening for the ideal antibody for detecting P400. This approach proved fruitful because the group was able to use this antibody to purify endogenous P400 and determine its sequence. Furthermore, they also observed that P400 binds IP3. These observations came around the time when IP3 was discovered as a messenger molecule that relays signals from cell-surface receptors to the intracellular environment.

Their results, together with published observations that calcium signaling is absent in Purkinje-cell-deficient mice, led Mikoshiba's team to conclude that P400 is the bona fide IP3 receptor that also functions as an intracellular calcium channel. Using various techniques in biochemistry, molecular biology, and microscopy, they were able to verify the receptor function *in vivo*, and demonstrate its localization at the endoplasmic reticulum where the intracellular calcium stores reside.

With his Rodbell statue in hand, Mikoshiba joined, left to right, Putney, Rodbell, and Birnbaum. (Photo courtesy of Steve McCaw)

The multi-faceted function of IP3 receptor

Since then, Mikoshiba has successfully identified three isoforms of IP3 receptor. Years of research by his team revealed that each isoform regulates a subset of cellular mechanisms, such as cell division, neuronal development, digestive functions, and protection against cellular stress. Therefore, it is not surprising that defects in the receptor or its expression result in a variety of health complications, including Huntington's disease, Sjogren's syndrome, and various autoimmune diseases.

Mikoshiba explained that while the IP3 receptor isoforms have similar protein sequences, they undergo modifications at different sites. The presence of several isoform-specific amino acids further distinguishes these isoforms from one another. “This could explain why the receptor is able to control such a broad spectrum of cellular activities,” he said. These distinctions are important in regulating IP3-binding affinity and channel opening, he added.

Analysis of the three-dimensional structure of IP3 receptor also revealed the presence of multiple cavities near the channel pore, rendering it a platform to which many downstream molecules can bind. Mikoshiba referred to it as a signaling hub that facilitates the interaction among various proteins and molecules in different cell types. “The different combinations of proteins that bind to the IP3 receptor help convert a simple IP3 wave into multiple downstream signals, which in turn regulate different cellular functions,” he concluded.

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

Speakers in the Dr. Martin Rodbell Lecture Series receive a statue depicting the hand of Nobel laureate and former NIEHS Scientific Director Martin Rodbell, Ph.D. , holding the three key elements involved in cell signaling. Sculptor Carl Regutti, who created the statue and attended the Rodbell lecture in 2012 as a family guest, died in April of this year. (Photo courtesy of Steve McCaw)

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